

Training and outreach portal of



Amoxicillin

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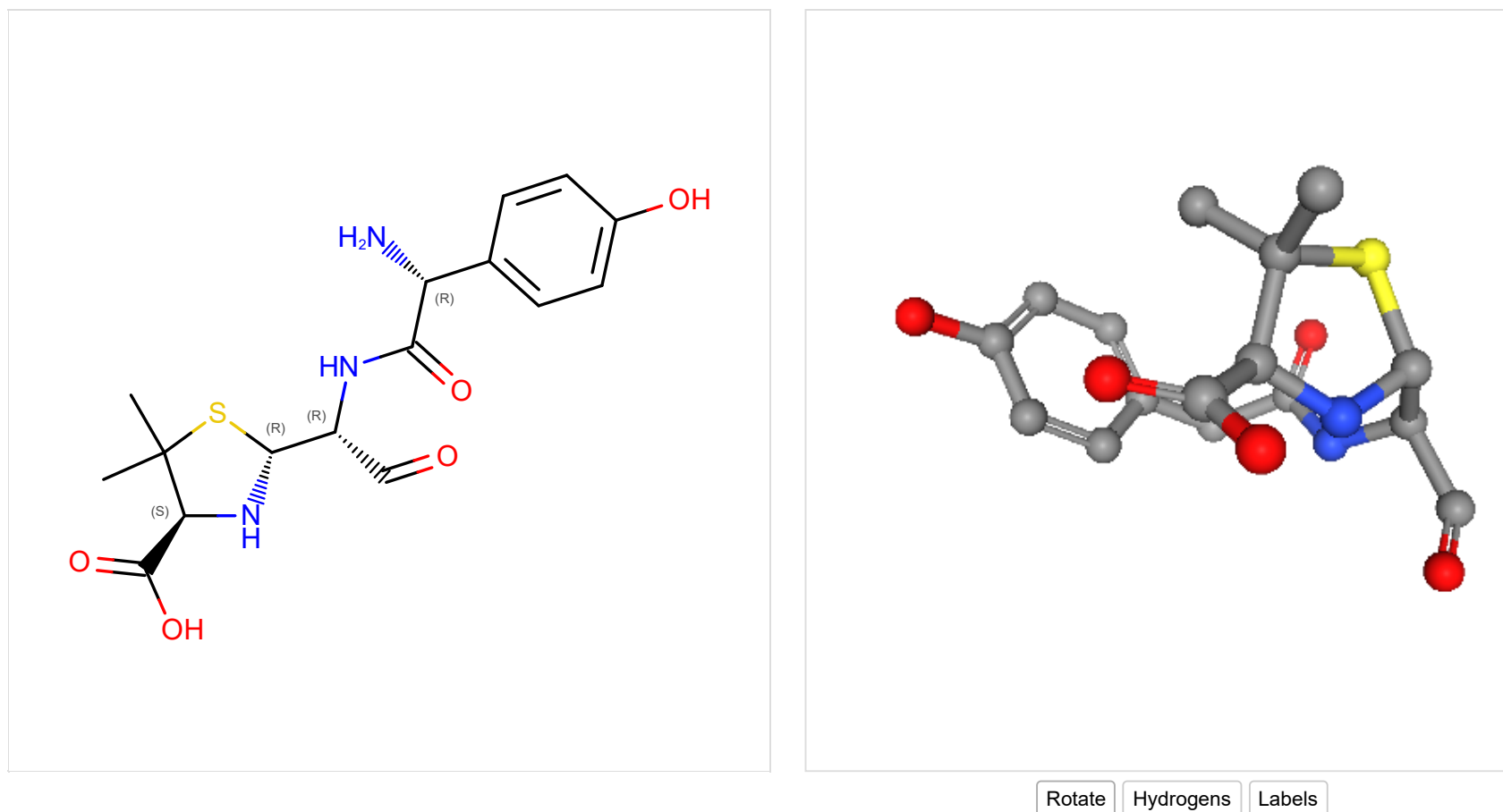
Drug Name

Amoxicillin belongs in the β -lactam class, specifically a penicillin G derivative used for the treatment of infections caused by gram-positive bacteria. It has similar activity to penicillin and ampicillin and was granted FDA approval in 1974. It competitively inhibits penicillin-binding proteins. Amoxicillin is frequently administered with Clavulanic acid.

Table 1. Basic profile of amoxicillin.

Description	Orally administered antibacterial drug
Target(s)	Penicillin-binding proteins (PBPs)
Generic	Amoxicillin
Commercial Name	Amoxil, Augmentin, Clavulin, Moxatag, Omeclamox, Prevpac, Talicia
Combination Drug(s)	Augmentin (Amoxicillin and Clavulanic Acid)

Other Synonyms	Amox, p-Hydroxyampicillin
IUPAC Name	(2S,5R,6R)-6-[(2R)-2-amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid
Ligand Code in PDB	AXL (open form)
PDB Structure	6I1E (Penicillin-Binding Protein 3 in complex with amoxicillin)
ATC code	J01CA04



Antibiotic Chemistry

Amoxicillin has a β -lactam ring (shown in pink in Figure 2) fused to a five-membered thiazolidine ring (shown in orange in Figure 2).

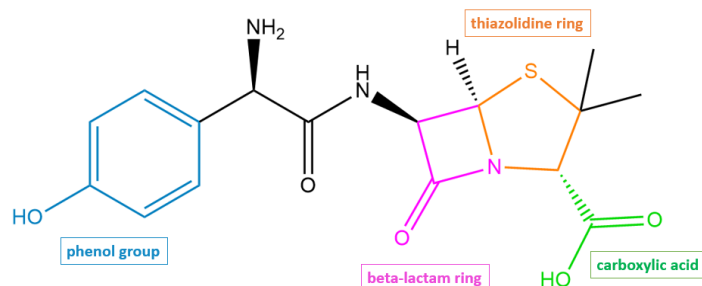


Figure 2. 2D structure of amoxicillin highlighting functional moieties responsible for antibacterial activity. Structure created using ChemDraw.

Drug Information

Table 2. Chemical and physical properties (DrugBank).

Chemical Formula	C ₁₆ H ₁₉ N ₃ O ₅ S
Molecular Weight	365.404 g/mol
Calculated Predicted Partition Coefficient: cLogP	0.75
Calculated Predicted Aqueous Solubility: cLogS	-2.6
Solubility (in water)	0.958 mg/mL
Predicted Topological Polar Surface Area (TPSA)	132.96 Å ²

Drug Target

Amoxicillin is an orally administered drug that disrupts cell wall biosynthesis in bacteria by binding to and inhibiting the penicillin-binding protein (PBP) enzymes. The name of this class of enzymes originates from the ability of penicillin and other β -lactam antibiotics to bind to these proteins. Some PBP enzymes are responsible for catalyzing the final steps of the peptidoglycan synthesis pathway, which include polymerizing glycan strands and then cross-linking adjacent chains to form the characteristic mesh structure of peptidoglycan, while other PBPs are involved in regulating peptidoglycan recycling and cell wall remodeling. Inhibition of the PBPs responsible for cross-linking results in a severely weakened cell wall, which then causes bacterial cell lysis and death. However, inhibition of PBPs involved only in peptidoglycan remodeling is non-lethal to the bacteria.

Learn more about PBPs.

Here we will examine the binding of amoxicillin to PBP-3 from *P. aeruginosa*. The enzyme is made of two domains (Han et al., 2010, Figure 3):

- * N-terminal domain (blue)

- * Penicillin-binding domain aka C-terminal Domain (pink) has the active site where β -lactam antibiotics, such as amoxicillin, bind.

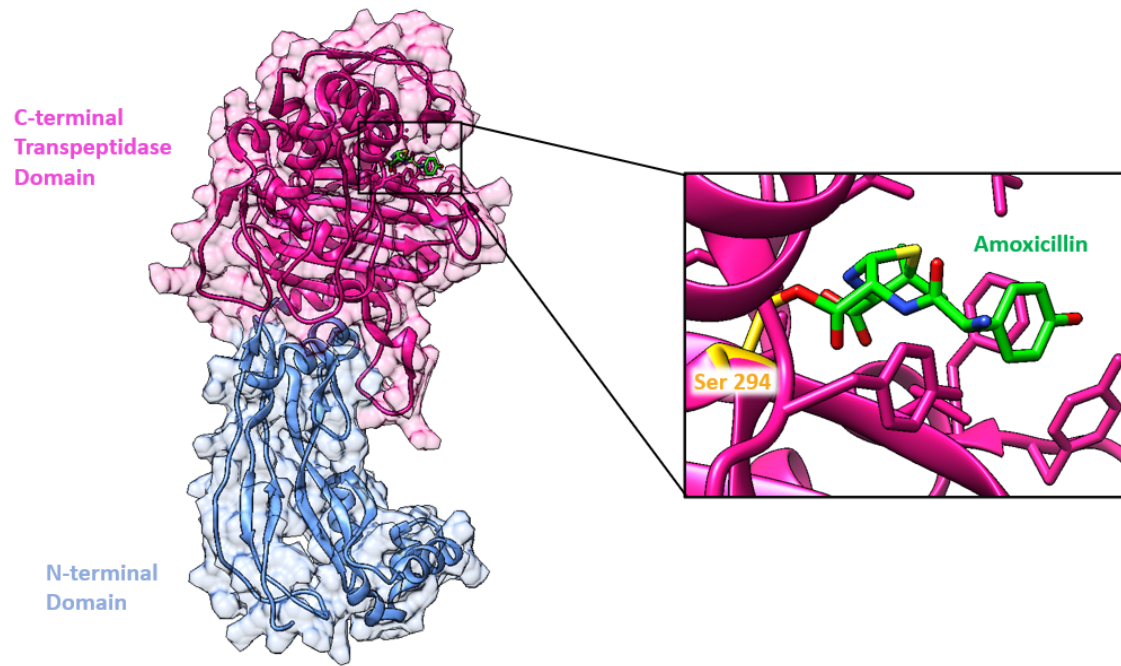


Figure 3. Ribbon representation of PBP3 bound to amoxicillin (color-coded atomic stick figure: C-spring green, N-blue, O-red, S-yellow). The inset shows the covalent linkage that forms between amoxicillin and Ser294 (color-coded atomic stick figure: C-gold, O-red). (PDB ID: 6I1E; van Berkel et al., 2013).

Drug-Target Complex

PBP3 serves as a transpeptidase during peptidoglycan synthesis in *P. aeruginosa* cells. This means that in the absence of amoxicillin, PBP3 is able to catalyze cross-linking between the peptide substituents on the glycan strands to form the mesh-like structure of peptidoglycan. It is a monofunctional enzyme because it is only involved in cross-linking, or transpeptidation, not in polymerizing the nascent glycan strands, a process known as transglycosylation. The Ser294 nucleophile is where the D-Ala-D-Ala peptide bond of the peptide substrate binds in the active site and takes part in the transpeptidation reaction.

[Click here to learn more about PBP3.](#)

Amoxicillin is able to bind to and inhibit PBP3 due to the structural similarity it shares with the terminal D-Ala-D-Ala peptide bond of the natural substrate. Specifically, the β -lactam ring, which is characteristic of all β -lactam antibiotics, is a structural mimic of the backbone of the D-Ala-D-Ala peptide, allowing the antibiotic to occupy the same binding site as the natural substrate.

The antibiotic reacts with the Ser294 nucleophile and forms an acyl-enzyme covalent complex (Figure 2). As the β -lactam blocks the Ser294 residue, the natural peptide substrate can no longer access the active site of PBP3. Thus, amoxicillin inactivates the enzyme and prevents transpeptidation.

The position of the ester linkage in the amoxicillin-bound complex is very similar to that of other β -lactams that bind to PBP3. The ester linkage in amoxicillin, along with the carbonyl oxygen of the β -lactam ring, forms a hydrogen bond with the main chain NH of Thr487. The carboxylic acid forms hydrogen bonds with the side and main chains of Ser485 and the side chain of Lys484. The β -lactam ring forms a hydrogen bond with Ser349. The drug also forms hydrogen bonds with Tyr409 and Asn351. These residues are indicated in Figure 4.

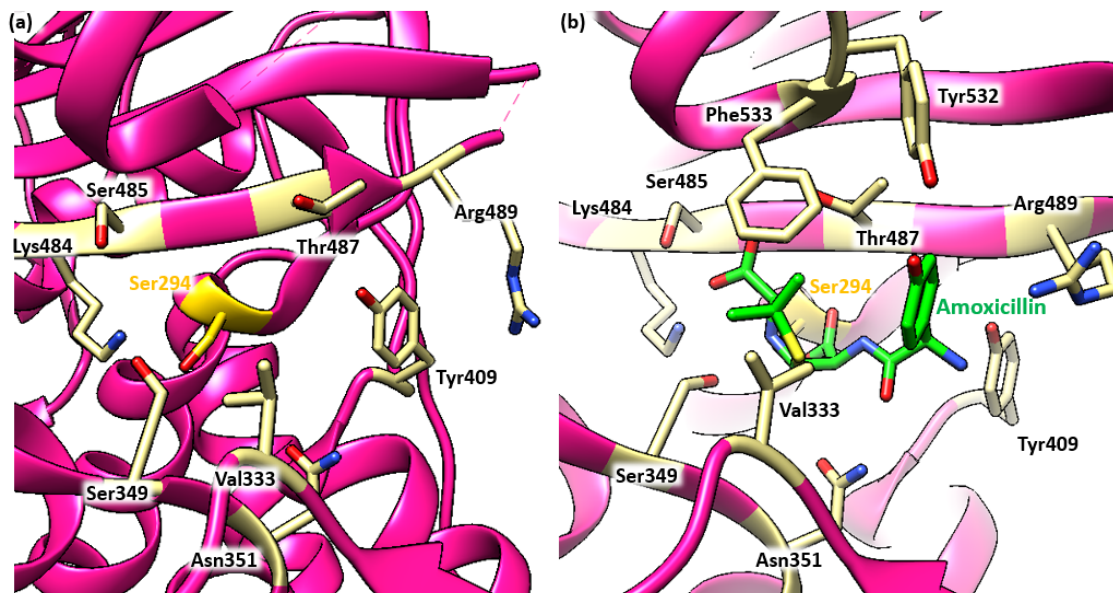


Figure 4. (a) Ribbon representation of the active site in the apoenzyme structure of PBP3 (PDB ID: 3oc2; Sainsbury et al., 2011). (b) Ribbon representation of the PBP3 active site after amoxicillin binding (PDB ID: 4kqo; Bellini et al., 2019). Color-coded atomic stick figure: C-khaki, O-red.

Pharmacologic Properties and Safety

Table 3. Pharmacokinetics: ADMET of amoxicillin.

Features	Comment(s)	Source
Oral Bioavailability (%)	60%	DrugBank
IC50	0.012 µg/mL (for binding to PBP3 in <i>S. pneumoniae</i>)	(Kocaoglu and Carlson, 2015)
Ki (µM)	N/A	N/A
Half-life (hrs)	1 hour	DrugBank
Duration of Action	8 to 12 hours	FDA

Features	Comment(s)	Source
Absorption Site	N/A	N/A
Transporter(s)	Renal organic cation transporter	DrugBank
Metabolism	Incubation with human liver microsomes has led to the detection of 7 metabolites	DrugBank
Excretion	~ 70 to 78% of amoxicillin is eliminated via urine after 6 hours	DrugBank
AMES Test (Carcinogenic Effect)	Probability 0.9099 (Non AMES toxic)	DrugBank
hERG Safety Test (Cardiac Effect)	Probability 0.9996 (weak inhibitor)	DrugBank
Liver Toxicity	Highly likely but rare cause of clinically apparent liver injury The cause of the liver injury associated with amoxicillin use is probably hypersensitivity or allergy.	LiverTox

Drug Interactions and Side Effects

Table 4. Drug interactions and side effects of amoxicillin.

Features	Comment(s)	Source
Total Number of Drug Interactions	37 drugs	Drugs.com
Major Drug Interaction(s)	bcg; cholera vaccine, live; methotrexate; typhoid vaccine, live	Drugs.com
Alcohol/Food Interaction(s)	N/A	N/A

Features	Comment(s)	Source
Disease Interaction(s)	Colostridioides difficile associated diarrhea (CDAD) (major), Mononucleosis (moderate), Diabetes (moderate), Renal dysfunction (moderate), Hemodialysis (moderate)	Drugs.com
On-target Side Effects	N/A	N/A
Off-target Side Effects	Diarrhea, nausea, skin rash, abdominal pain, vulvovaginal mycotic infection, headache, taste perversion, candidiasis, fungal/mycotic infection	Drugs.com
CYP Interactions	Non-substrate	DrugBank

Links

Table 5: Links to learn more about amoxicillin

Comprehensive Antibiotic Resistance Database (CARD)	ARO: 0000064
DrugBank	DB01060
Drugs.com	https://www.drugs.com/amoxicillin.html
FDA	https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/50542s02950754s01950760s01950761s016lbl.pdf
LiverTox: National Institutes of Health (NIH)	https://www.ncbi.nlm.nih.gov/books/NBK547854/
PubChem CID	33613

Learn about amoxicillin resistance.

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Amoxicillin. PubChem. <https://pubchem.ncbi.nlm.nih.gov/compound/33613>

Amoxicillin - DrugBank. Drugbank.ca <https://go.drugbank.com/drugs/DB01060>

Amoxicillin. Drugs.com <https://www.drugs.com/amoxicillin.html>

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LiverTox - Clinical and Research Information on Drug-Induced Liver Injury. National Institutes of Health.
<https://www.ncbi.nlm.nih.gov/books/NBK547854/>

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https://doi.org/10.2210/rcsb_pdb/GH/AMR/drugs/antibiotics/cellwall-biosynth/pbp/blm/amoxicillin